DIAGNOSTIC DIFFICULTIES IN MILD HAEMOPHILIA AND CHRISTMAS DISEASE

BY

BARBARA M. FESSEY, M. J. MEYNELL, AND W. T. COOKE

From the General Hospital, Birmingham

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Two cases of haemorrhagic diathesis are described, where the laboratory diagnosis was confused owing to previous blood transfusions.

Without the help of investigating the relatives, the nephew of Case 1, the haemophiliac, and the uncle of Case 2, with Christmas disease, there would have been considerable delay in reaching the diagnosis and so instituting the correct treatment.

Ordinarily the laboratory diagnosis of classical haemophilia (haemophilia A) and Christmas disease (haemophilia B, plasma thromboplastin component deficiency) is easy using the thromboplastin generation test as described by Biggs and Douglas (1953). Nevertheless difficulty arises when the patient mildly deficient in anti-haemophilic globulin or Christmas factor is transfused following haemorrhage.

The concentration of the deficient factor may be raised for a variable period above 30% with fresh whole blood or plasma, a level capable of producing a normal result with the thromboplastin generation test. The length of this interval is dependent on a number of factors which include the initial anti-haemophilic globulin level of the patient (between 5 and 25% in the mildly affected), the anti-haemophilic globulin content of transfused blood or plasma, the half-life of anti-haemophilic globulin (eight to ten hours), and the increased rate of utilization associated with haemorrhage. These comments are even more applicable in mild Christmas disease since the clotting factor is more stable and may last in the circulation for several days.

In hospital practice this difficulty in distinguishing abnormalities of mild degree causes therapeutic problems. To clarify the diagnosis repeated quantitative assays would be of value, but all methods are time consuming, some require special reagents, and others a constant source of the same plasma as a reference standard. Also the time necessary for the degradation of transfused anti-haemophilic globulin or Christmas factor will delay correct treatment; often it is not possible to postpone transfusion in order to permit the laboratory to make the correct diagnosis.

Although Hicks and Pitney's screening test (1957) is said to be more sensitive than the standard thromboplastin generation test, it does not differentiate between haemophilia and Christmas disease. It is now accepted that the degree of deficiency of the clotting factor in haemophilia and in Christmas disease is the same in the affected members of a family, i.e., if there is 5% or less anti-haemophilic globulin all will have the same concentration and be severe haemophiliacs. In between 5 and 25% the condition is considered mild and all affected members have mild haemophilia. Classical haemophilia and Christmas disease are inherited as sex-linked Mendelian recessives. With a carrier mother the daughters have a 50% chance of being carriers, and the sons the same chance of being bleeders. With a haemophiliac father all daughters will be carriers and the sons normal, i.e., neither carriers nor sufferers. With this in mind the relevant members of a family may be investigated by a planned approach.

The purpose of this short paper is to demonstrate the value of investigating the relatives of such patients.

Case Reports

Case 1.—Mr. G. C., aged 64, a blacksmith, was admitted to another hospital on October 31, 1955, complaining of two attacks of painless haematuria, one 18 months and the other nine days before admission. He had been in fairly good health and gave no history of excessive bleeding.

Examination revealed an enlarged prostate; biochemical investigations proved satisfactory and a prostatectomy was performed. Eleven days after, on November 21, the suprapubic wound was found to be leaking urine and the bladder was distended with large

blood clots. These were removed, but the condition recurred a week later. The patient had been given 4 pints of blood during the first operation and a further 6 pints during the following 20 days.

He was admitted to the General Hospital, Birmingham, on November 30, 1955, for further investigations after having a total of 10 pints of blood, 2 of these on the day before admission. On close questioning, he admitted that he bled excessively following dental extractions, and that his nephew (a sister's son) was similarly affected. Haematological investigations on admission had revealed no abnormality, when the haemoglobin was 81% (12.0 g.%), red blood cells 3,980,000 per c.mm., white blood cells 5,600 (normal differential), platelets 370,000 per c.mm., Hess's test negative, bleeding time (Ivy's method) 1½ minutes, clotting time (37° C., Lee and White) 8½ minutes, prothrombin level (Quick's one-stage method) 100%, clot retraction normal. The thromboplastin generation test gave a normal result (Table I).

TABLE I
FIRST THROMBOPLASTIN GENERATION TEST ON CASE I

Reagents	Incubation Time (min.)					
	1	2	3	4	5	6
<i>Using normal platelets</i>						
(1) Normal serum and normal adsorbed plasma	86	53	14	13	13	13
(2) Patient's serum and patient's adsorbed plasma	75	37	14	13	13	13
(3) Normal serum and patient's adsorbed plasma	84	50	16	15	14	14
(4) Patient's serum and normal adsorbed plasma	70	16	12	13	12	13
<i>Using patient's platelets</i>						
Normal serum and normal adsorbed plasma	62	34	15	13	13	12

Two days later the haemoglobin fell to 68% (10.1 g.%). The suprapubic wound was still leaking, so the bladder was reopened and again found to be distended with clotted blood; no bleeding point was discovered. Continuous irrigation of the bladder was begun and 3 pints of stored blood transfused. Four days later a further 3 pints were given and on the following day all bleeding ceased only to restart after

TABLE II
SECOND THROMBOPLASTIN GENERATION TEST ON CASE I

Reagents	Incubation Time (min.)					
	1	2	3	4	5	6
<i>Using normal platelets</i>						
(1) Normal serum and normal adsorbed plasma	45	20	15	16	15	15
(2) Patient's serum and patient's adsorbed plasma	49	32	27	26	20	22
(3) Normal serum and patient's adsorbed plasma	50	35	25	25	25	28
(4) Patient's serum and normal adsorbed plasma	45	15	15	16	16	15
<i>Using patient's platelets</i>						
Normal serum and normal adsorbed plasma	52	18	15	15	13	15

an interval of three days. A repeat thromboplastin generation test taken five days following the last blood transfusion showed a definite pattern of mild haemophilia (Table II). Unfortunately before this abnormal result could be confirmed, the patient's general condition deteriorated rapidly and a cystoscopy was performed. Blood was seen coming from the right-sided ureteric orifice and a right-sided nephrectomy was carried out. After this, bleeding occurred into the nephrectomy wound and was controlled by the application of fresh pork fat. He was given a further transfusion of 4 pints of blood and improved. Macroscopic examination of the kidney revealed no bleeding point; sections showed a moderate degree of pyelonephritis.

On December 20 investigations of the patient's nephew (A. F.), who had previously refused to come to hospital, showed that he bruised easily, bled excessively after dental extractions, and had had haemorrhage into the joints as a child. The result of the thromboplastin generation test showed that he was mild haemophilic (Table III). The third thrombo-

TABLE III
THROMBOPLASTIN GENERATION TEST ON NEPHEW OF CASE I

Reagents	Incubation Time (min.)					
	1	2	3	4	5	6
<i>Using normal platelets</i>						
(1) Normal serum and normal adsorbed plasma	47	15	15	15	16	16
(2) Patient's serum and patient's adsorbed plasma	57	37	29	37	39	28
(3) Normal serum and patient's adsorbed plasma	47	38	40	46	38	45
(4) Patient's serum and normal adsorbed plasma	35	19	18	15	15	15
<i>Using patient's platelets</i>						
Normal serum and normal adsorbed plasma	30	17	15	14	15	15

plastin generation test on the patient, seven days after his last transfusion, then confirmed the anti-haemophilic globulin deficiency (Table IV).

The patient was then treated as a case of haemophilia with transfusions of fresh blood and plasma. No concentrated anti-haemophilic globulin

TABLE IV
THIRD THROMBOPLASTIN GENERATION TEST ON CASE I

Reagents	Incubation Time (min.)					
	1	2	3	4	5	6
<i>Using normal platelets</i>						
(1) Normal serum and normal adsorbed plasma	32	14	15	17	15	15
(2) Patient's serum and patient's adsorbed plasma	45	25	20	19	20	19
(3) Normal serum and patient's adsorbed plasma	43	23	24	24	21	28
(4) Patient's serum and normal adsorbed plasma	35	20	16	15	15	15
<i>Using patient's platelets</i>						
Normal serum and normal adsorbed plasma	48	17	15	14	13	15

of human or animal origin was available at that time. Despite antibiotic treatment, he developed bronchopneumonia and died on January 9, 1956. At necropsy the remaining kidney showed pyelonephritis.

Case 2.—Mr. G. P., aged 26, a storekeeper, was admitted to another hospital on October 26, 1959, after a haematemesis. Because of a history of a tendency to bleed easily he was transferred to the General Hospital, Birmingham, three days later for further investigation after the transfusion of 9 pints of blood. He had always bruised readily and bled excessively after dental extractions. At 12 years of age he was transfused with 4 pints of blood following the extraction of one tooth. He had had a haematemesis and melaena three years before for which no treatment was given. He had a married sister with no children and one unmarried brother, who were quite normal. However, an uncle, his mother's brother, was said to bleed excessively. Laboratory investigations of the patient showed that the haemoglobin was 71% (10.6 g.%), white blood cells 7,400 per c.mm., platelets 104,000 per c.mm.; Hess's test, prothrombin level, and clot retraction were normal. The bleeding time was three minutes at 37° C. (Lee and White's method). A thromboplastin generation test was indecisive (Table V) and the

TABLE V
THROMBOPLASTIN GENERATION TEST ON CASE 2

Reagents	Incubation Time (min.)					
	1	2	3	4	5	6
<i>Using normal platelets</i>						
(1) Normal serum and normal adsorbed plasma ..	23	11	14	16	12	13
(2) Patient's serum and patient's adsorbed plasma ..	23	12	13	16	14	16
(3) Normal serum and patient's adsorbed plasma ..	13	10	12	10	13	13
(4) Patient's serum and normal adsorbed plasma ..	24	17	19	18	18	22
<i>Using patient's platelets</i>						
Normal serum and normal adsorbed plasma ..	21	15	13	14	13	12

repeat gave a similar abnormal but non-diagnostic result. It was thought that he had mild Christmas disease, and that the thromboplastin generation test did not give a typical pattern because of the previous blood transfusion.

Investigations of his uncle, aged 60, showed that he too had bled excessively following dental extrac-

tions, usually necessitating plugging. Haematological investigations were quite negative, but a thromboplastin generation test revealed the presence of mild Christmas disease (Table VI). It was assumed that

TABLE VI
THROMBOPLASTIN GENERATION TEST ON UNCLE OF CASE 2

Reagents	Incubation Time (min.)					
	1	2	3	4	5	6
<i>Using normal platelets</i>						
(1) Normal serum and normal adsorbed plasma ..	60	15	9	10	9	8
(2) Patient's serum and patient's adsorbed plasma ..	70	19	16	20	16	15
(3) Normal serum and patient's adsorbed plasma ..	10	7	10	10	8	9
(4) Patient's serum and normal adsorbed plasma ..	40	20	25	24	23	28
<i>Using patient's platelets</i>						
Normal serum and normal adsorbed plasma ..	24	14	11	10	10	9

the patient G. P. was similarly affected, and he was treated by transfusing 7 pints of blood. He made a rapid recovery and was sent home on November 9. Two weeks later a repeat thromboplastin generation

TABLE VII
REPEAT THROMBOPLASTIN GENERATION TEST ON CASE 2

Reagents	Incubation Time (min.)					
	1	2	3	4	5	6
<i>Using normal platelets</i>						
(1) Normal serum and normal adsorbed plasma ..	90	60	16	13	15	14
(2) Patient's serum and patient's adsorbed plasma ..	120	80	35	33	27	28
(3) Normal serum and patient's adsorbed plasma ..	90	62	20	15	15	14
(4) Patient's serum and normal adsorbed plasma ..	95	52	37	32	30	29
<i>Using patient's platelets</i>						
Normal serum and normal adsorbed plasma ..	20	15	14	13	12	12

test clearly confirmed that he was a case of Christmas disease (Table VII). A barium meal as an out-patient showed a duodenal ulcer; he was placed on an ulcer regime and up to date is well.

REFERENCES

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